REMARKS

Amendment to Claims

Applicants have amended the claims by removing the terminology "exhibiting similar functionality" because the Office found the terms to be indefinite. Applicants moved some text around so that the functionality which was already in the claims is now clearly recited at a different section in the independent claims 1 and 74. Applicants have not entered any new matter that has not already been searched and examined. Moving text in a claim cannot be considered to be new matter, thus no new matter has been added.

Rejections of Claims and Traversal Thereof

In the March 15, 2007 Office Action,

claims 1-3, 6-9, 11, 13-16, 24, and 73-85 were rejected under U.S.C. §112, first and second paragraphs.

Applicants traverse these rejections and submit that all claims, as now amended, meet the requirements of U.S.C. §112, first paragraph and second paragraphs.

Rejection under U.S.C. §112, second paragraph

Claims 1 and 74 have been rewritten to recite the functionality of the modified sequences. Applicants submit that the amendment to the claims obviates the rejection and request the withdrawal of the rejection under U.S.C. §112, second paragraph.

Rejection under U.S.C. §112, first paragraph

In the March 15, Office Action, the Office maintained the rejection of claims 1-3, 6-9, 11, 13-16, 24, and 73-85 under U.S.C. §112, first paragraph for failing to comply with the enablement requirements.

Notably, in the previous Office Action of September 15, 2006, the Office stated that:

> "While the specification provides the evidence that gp120-CD4 chimeric molecules, containing a CCR5-specific HIV envelope bind to and block CCR5 receptor, the specification provides no exemplification of a chimeric polypeptide, which amino acid sequence is a truncated or modified, forming an intramolecular complex and interacting with or blocking a cellular co-receptor that is utilized by a virus for infection."

Applicants are very concerned that the Office missed some very important data and guidance as set forth in the specification and specifically the following examples that show such evidence.

Initially Example II should be reviewed for evidence showing that both the full length and truncated sequence formed the binding complex. Specifically, Example II describes data demonstrating that the binding of gp120 to CD4 causes conformational changes in the molecule leading to the exposure of the co-receptor-binding domain which is referred to herein as the cryptic epitope. Therefore, antibodies directed against the cryptic epitopes, wherein the cryptic epitope binds to the CCR5 receptor, should react strongly with properly folded single-chain molecules. In order to determine that binding occurred between the formed cryptic and exposed epitopes in the chimeric molecules, antigenic properties of FLSC and TcSC molecules were compared. Purified FLSC and TcSC were subjected to immunochemical analyses by antigen capture ELISA. Detection was also accomplished using monoclonal antibodies (Mabs A32, 17b and 48d) previously shown to preferentially **bind gp120 after engagement of CD4** (M. Thali *et al., J. Virol.*, 67:3978-86 (1993)), followed by the appropriate-labeled second antibody. In order to evaluate the TcSC antigen which lacks the D7324 epitope, an alternate ELISA format using anti-CD4 Mab 45 (Bartels, Issaquah, WA) for capture was developed. The antibody was adsorbed to plastic at 1 ug/ml and wells blocked with BLOTTO. Assays were then carried out as above using the indicated human sera or human monoclonal antibodies.

As shown in FIG. 5A, all of the antibodies that react with the cryptic epitopes (co-receptor binding) reacted strongly with the FLSC. The half-maximal binding concentrations of antibodies 17b, 48d, and A32 were consistently higher with FLSC versus gp120 alone, and equivalent to what was observed with soluble, non-covalent BaLgp120-rsCD4 complexes. As shown in FIG. 5B, the level of 17b and 48d reactivity with TcSC was equivalent to what was observed with FLSC analyzed in parallel.

In sum, **these data indicate that the single-chain gp120-CD4 molecules (both full length and truncated) formed interacting complexes similar to the transition state HIV envelope-CD4 complex and exposed epitope that bind to the co-receptor**.

Additionally, applicants have provided such evidence in Example VII that describes data demonstrating that mutation of the furin cleavage site improves the stability of the FLSC complex. (This mutation would qualify the sequence as having at least 95% identity to the full-length sequence). Notably, the specification clearly states that cleavage of the FLSC at the natural furin site would be consistent with the behavior of the FLSC fragments, as it would have minimal impact on the structures of the gpl20 and CD4 moieties and their capacity to interact. The results in FIG. 13 show that mutation of the furin cleavage site prevents the gp120 found on the FLSC R/T from dissociating as readily as the cleaved FLSC, thus improving its stability of the FLSC R/T complex. Notably, one skilled in the art can easily determine the ability of **the modified sequence to** form the intramolecular complex by using the testing methods of Example III by determining the level of binding of the 17b antibody or in alternative competitive ELISA with soluble CD4.

In total applicants have already provided exactly what the Office contends is lacking support in the specification, that being ,evidence that full length, truncated and modified sequences have the functionality of forming an intramolecular complex that allows for binding with a co-receptor.

In light of this clear evidence as expressly stated in the specification, applicants question why the claims were found to be non-enabling.

Further, the Office states that one skilled in the art would not know how to truncate the full length sequence and which sequences should be deleted to achieve either the truncated sequence of having 95% identity. Importantly, claim 1 recites that "**and the viral cell surface receptor polypeptide sequence and the virus coat polypeptide sequence comprises amino acid residues of the region having binding-affinity for each other**" Thus, applicants have provided guidance and instruction for inclusion of important residues. Applicants insist that one skilled in the art would recognize that certain residues in either binding partner are important for binding.

Further, applicants believe that the Office is overlooking the knowledge of one skilled in the art at the time of filing of the present invention. Firstly, the HIV virus has been studied since the early 80s when Dr. Robert Gallo (one of the first investigators) discovered that AIDS was caused by the HIV virus (Appendix A). Since that time, a multiplicity of investigators have studied the virus's interaction with the corresponding cell receptors. For example, in the Declaration filed by Dr Devico, back in December 2003, he discussed the interaction of gp120 with the binding receptor partner CD4. Specifically, Dr. Devico reiterated knowledge known at the time of filing relating to the structure of the gp120-CD4 complex. Specifically, the interaction between CD4 and gp120 involves main-chain (at least half the interactions) and side chain atoms. The hot spot on gp120 is a deep, roughly spherical pocket that accommodates Phe 43 located on the CD4 CDR2 loop. The gp120 pocket is lined with highly conserved residues. Direct interatomic contacts between CD4 and gp120 seem to involve some 22 CD4 residues and 26 gp120 residues. These include 219 van der waals contacts and 12 hydrogen bonds. The Ph e43 (on CD4) and Arg 59 of CD4 engages in interactions with a Asp 368, Glu 370, Trp 427, Gly 473 in the gp120 pocket as does a CD4 59Arg with a gp120 Val 430. Applicants can provide numerous references if the Office needs to be convinced that this knowledge was available to undergraduates studying virology at the time of filing of the present application.

Thus, the statement by the Office that one skilled in the art would not know how to truncate the chimeric polypeptide and how to achieve the 95% identity is unfounded. Instead applicants insist that one skilled in the art would recognize that certain residues in either of the binding partner are important for binding. Clearly, one skilled in the art would avoid deleting residues that have been found to be important in the binding complex between gp120 and CD4. For example there is limited binding residues on the N and C terminal of gp120 for CD4, and as such, such residues can be deleted without substantially affecting the binding between the ligand and receptor (Lasky 1987 and Pollard 1992, Appendix A).

It is well settled in the law that an application does not need to include that which was known at the time of filing by those skilled in the art. If this was not true then every application would have to be the size of a PhD dissertation. Thus, applicants did not need to include such information in the application relating to residues that could be deleted or substituted.. Further the fact that there must be

some experimentation to determine the level of binding affinity in the intramolecular binding complex of the present invention does not mean that the experimentation is undue.

Notably nearly all the *Wands* factors weigh in favor for enablement in this case. Claim 1 and 74 are limited to the viral coat proteins of HIV and interacting cell receptors and such components have the ability to form intramolecular complexes. As discussed, one skilled in the art at the time of the filing of the application would understand that there are specific residues important for the formation of such binding complex. As such, the claims are not too broad of scope and there would not be undue experimentation to verify such functionality. Again as stated above, the specification provides ample guidance for determining such functionality by the numerous working examples in the specification. Further, numerous investigator have determined the important residues that contribute to the formation of the binding between the cell receptor and viral coat polypeptide. As such, this knowledge contributes to the enablement of this invention and increases the degree of predictability. Finally, the level of skill in the art is relatively high in the field of molecular biology. Thus, the *Wands* factors indicate that the specification **does** provide sufficient disclosure to enable those skilled in the art to practice the full scope of the claims without undue experimentation.

Applicant submits that the instant application provides sufficient and enabling information for a person of ordinary skill in the art to practice applicants' invention and respectfully requests the withdrawal of all rejections under §112, first paragraph.

Rejoining of Method Claims

Applicants are requesting that all method and use claims that are currently withdrawn be rejoined and examined according to the guidelines set forth in Section 821.04 of the MPEP.

Applicants have included herewith a Declaration by Dr. Devico (Appendix B, both executed and an unexecuted "word" document for ease of reading) which provides additional evidence of the effectiveness of the present chimeric polypeptides to induce the production of neutralizing antibodies.

Specifically, the results show that the chimeric polypeptides form neutralizing antibodies. Rhesus macaques were immunized with a gp120-CD4 single chain that used rhesus CD4 in lieu of human

CD4 thereby allowing evaluation of the concept in an autologous CD4 background. This allowed the mimicking of what would occur if FLSC was in humans. The study also included a group of naïve animals and control groups that received either $gp120_{BaL}$ or soluble human CD4 alone. This study also included a rectal challenge with the heterologous R5 $SHIV1_{162P3}$ to assess whether these responses would be in any way protective. Notably, after three immunizations (week 26), the majority of the complex-immunized macaques had circulating titers of neutralizing antibodies.

At week 115, the animals were boosted, then, on week 119, challenged rectally with the heterologous R5 $SHIV1_{162P3}$. The resulting viral loads were tracked until week 135. Notably, all animals vaccinated with rhFLSC exhibited accelerated clearance of plasma viremia and stronger suppression of tissue viremia compared to naïve controls and the other immunization groups. The single chain complexes elicited broadly neutralizing antibodies. Thus, the single chain complex emerged as an envelope-based immunogen that has been used as a single subunit vaccine to afford protection against mucosal infection with a heterologous SIV. These studies also raise the possibility that broadly neutralizing antibody responses (as detected by in vitro assays) might not be the only immunogenic feature of constrained gp120 structures. As such, Dr. Devico has shown that the chimeras of the present invention have been found effective to raise neutralizing antibodies in an in vivo subject.

Conference with Examiner, Primary Examiner and Supervisor

Applicants are filing this response within the two month period of receiving the final office action. Applicants request that the Office immediately address this response so that a decision can be prepared by the Patent Office by the June 15, 2007 three month deadline. In the event that the Office does not issue a Notice of Allowance on these claims, applicants request that a conference be arranged between the Examiner, Primary Examiner, current Supervisor and the inventors of the present invention. Additionally, applicants would request that Dr. Robert Gallo be allowed to join this conference in light of the fact that he is an expert in this field and has been involved in the investigation of the science included in the application.

As such, applicants are again requesting that this response be reviewed and a decision made by the Patent Office by June 15, 2007, so that there is ample time to meet with the Assistant Examiner Boesen, the current Primary Examiner and the current Supervisor.

Fees Payable

Applicants believe that no fee is due for entry of this amendment. In the event a fee is found due, the Commissioner is authorized to charge such amount due to Deposit Account No. 13-4365.

Conclusion

Applicant has satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Boesen reconsider the patentability of all pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Boesen is requested to contact the undersigned attorney at (919) 286-8089 to resolve same.

Respectfully submitted,

Marianne Fuierer
Attorney for the Applicants
Registration No. 39,983

Moore & Van Allen, PLLC
P. O. Box 13706
Research Triangle Park, NC 27709
Telephone: (919)-286-8089
Fax: (919)-286-8199